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Epstein-barr viruses (EBVs) deficient in EBV-encoded RNAs have higher levels of latent membrane protein 2 RNA expression in lymphoblastoid cell lines and efficiently establish persistent infections in humanized mice

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Abstract: Functions of Epstein-Barr virus (EBV)-encoded RNAs (EBERs) were tested in lymphoblastoid cell lines containing EBER mutants of EBV. Binding of EBER1 to ribosomal protein L22 (RPL22) was confirmed. Deletion of EBER1 or EBER2 correlated with increased levels of cytoplasmic EBV LMP2 RNA and with small effects on specific cellular microRNA (miRNA) levels, but protein levels of LMP1 and LMP2A were not affected. Wild-type EBV and EBER deletion EBV had approximately equal abilities to infect immunodeficient mice reconstituted with a human hematopoietic system.

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Epstein Barr viruses deficient in EBER RNAs give higher LMP2 RNA expression in lymphoblastoid cell lines and efficiently establish persistent infection in humanised mice

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ABSTRACT

Lymphoblastoid cell lines made with recombinant B95-8 Epstein-Barr Virus (EBV) lacking EBER RNA expression were used to test various proposed functions of the EBER RNAs in a more physiological context than has been studied previously. The binding of EBER1 to RPL22 was confirmed but there was no significant effect of this on p53 expression or the response of p53 to cisplatin treatment. Deep sequencing and qPCR analysis of cellular miRNAs showed no evidence for miRNAs derived from the EBER sequences and minimal effects on cellular miRNA levels in response to deletion of EBER1 or EBER2. However, deletion of EBER1 or EBER2 correlated with increased cytoplasmic EBV LMP2 RNA and small changes in the T cell response were observed in immunodeficient mice reconstituted with a human haematopoietic system. The approximately equal ability of wild type and EBER deletion EBV to infect these humanized mice indicates that this could provide a system to identify physiological functions of the EBER RNAs.

IMPORTANCE

The EBER RNAs are some of the most abundantly expressed genes of Epstein-Barr Virus (EBV) and are routinely used as a diagnostic marker for EBV infection but their molecular functions remain unclear. Here we use EBV mutated in the EBER genes to test various proposed functions for EBER RNAs in a more physiological setting than used previously. We demonstrate effects on levels of EBV LMP2 RNA and cell miRNAs. We also show that the mutated viruses can infect immunodeficient mice reconstituted with a humanised haematopoietic system, demonstrating an in vivo system in which the functions of EBER RNAs can be explored.

INTRODUCTION

Epstein-Barr virus (EBV) encoded RNAs (EBERs) are the most abundant viral non-coding RNAs in EBV transformed lymphoblastoid cell lines (LCLs) but their physiological functions are still uncertain. Their strong expression during latent infection, with lower levels in the virus lytic cycle, suggests important roles for EBERs in EBV latency or persistence. EBER1 is 167nt and EBER2 is 173nt long and they are primarily located in the cell nucleus. Although there is evidence for the analogous VA RNAs of adenovirus partly being converted to miRNAs (1-3), deep sequencing of small RNA from EBV infected cells showed no evidence for processing of EBERs to make miRNAs (4). This did not exclude the possibility that EBERs might affect the levels or function of cell miRNA, as was observed for adenovirus VA RNAs (5).

EBERs have been linked to malignant phenotypes and tumour formation in immune-deficient SCID mice (6-8), and to resistance to apoptotic inducers and up regulation of the BCL-2 oncoprotein, which can protect BL-derived Akata cells from c-Myc-induced apoptosis (7, 9). Transgenic mice expressing EBERs in the lymphoid compartment were found to develop lymphoid hyperplasia and, in some cases, lymphoma (10). Cell genes whose expression in EBV LCLs correlates with deletion of EBER1 or EBER2 have been reported (11) but no specific mechanism has been identified. Most studies have focussed on cell intrinsic functions for EBERs but they have also been reported to be released from cells (12) and have been detected in exosomes (13).

EBER2 has been reported (14, 15) to be required for efficient transformation of B lymphocytes and maximum growth potential of LCLs, enhancing IL-6 expression to assist LCL growth (14, 15), but other studies using different EBV strains (11, 16) found EBERs not to be

65 required for primary infection, viral replication or efficiency of B cell immortalization.
66 Recently EBER2 has been shown to bind PAX5 and to promote PAX5 binding to a site in the
67 terminal repeat region of the EBV genome (17). Knockdown of EBER2 by an siRNA resulted
68 in raised RNA levels for EBV genes in that region of the genome, LMP1 and LMP2 (17).

69 EBER1 has for many years been known to bind to ribosomal protein L22 (RPL22) (18) and
70 has more recently been found to bind AUF1 (AU rich element binding factor 1), an RNA
71 binding protein (19). The binding of EBER1 to RPL22 was given new interest by studies on
72 RPL22 knockout mice (20). Mice lacking RPL22 develop to normal size and weight so,
73 although RPL22 is a component of the large ribosomal subunit, there was little indication for
74 RPL22 being crucial for protein synthesis. However, the adult RPL22 null mice specifically
75 lacked alpha beta T cells. Remarkably, RPL22 null mice that were also null for p53 were
76 found to have a normal blood count, indicating a p53 dependent loss of developing T cells in
77 the thymus (20). This suggested that there might be a role for RPL22 in a novel pathway
78 linking ribosomal function to p53. Further investigation of the RPL22 knockout mice (21)
79 revealed an analogous but less extreme phenotype in the B cell lineage, resulting in B cell
80 counts in the spleen about 30% of the normal level, the reduction being in the follicular B
81 cells. This p53 dependent defect was found to be present at the pro B cell stage, resulting in
82 lower levels of Pro B, Pre-B and other immature B cells in the bone marrow. In contrast, the
83 mature B cells from the RPL22 $-/-$ mice (although lower in number) responded normally to
84 LPS, anti-IgM or anti-CD40 and IL4 stimulation, showing no apparent defect at the mature B
85 cell stage (21). The effect is thought to be mediated by RPL22 binding to p53 mRNA,
86 reducing the translation of p53, and has been demonstrated independently in an
87 investigation of Miz1 regulation of p53 in B cells undergoing V(D)J recombination (22).

Possibly EBER1 could modulate this pathway in human B cells, although EBV infects mature B cells, in which no RPL22 phenotype was reported.

In this paper we use human LCLs infected with recombinant EBV strains lacking EBER1 or EBER2 to test for effects on RPL22 function, cellular miRNA levels and the levels of RNA encoding LMP1 or LMP2. We also show that mice with a humanised haematopoietic system can be infected by EBV lacking EBER genes, providing a system that can be used to investigate EBER function in a more physiological setting.

METHODS

Cell culture and EBV infections

Procedures for preparation of 293 cell clones carrying EBV-BACs, production of EBV, isolation of primary B-cells from buffy coats by negative selection with the RosetteSep Human B Cell Enrichment Cocktail (Stem Cell Technologies), titration of EBV stocks by detection of gfp in Raji cells and infection with EBV were all as described previously (11).

Transfection and western blotting.

Flag tagged RPL22 was expressed from pBK2-CMV in 293 cells by lipofectamine transfection, as described previously (11) and detected with M2 Flag monoclonal antibody (Sigma-Aldrich) at 1/2000 dilution. The pcDNA3.1 Flag-Schlafen plasmid was a kind gift of G. Brady (23). Expression of EBERs in 293 cells was from pHEBo-EBER1 or pHEBo-EBER2 (11). LCLs were transfected with the Neon electroporator using condition 16 (pulse voltage 1400V, width 20ms, number 2). DO1 antibody (Santa Cruz) was used for detection of p53 by Western blotting.

Deep sequencing and analysis of small RNAs

Total RNA was isolated from 10 individual LCLs (two wild-type, two EBER1KO, two EBER2KO, two EBER1rev, and two EBER2rev) using TRIzol (Invitrogen). Small RNAs (18-24 nt) were size-fractionated on 15% TBE-urea polyacrylamide gels and used to generate deep sequencing libraries as described in (24). Libraries were multiplexed and sequenced in one lane on the Illumina HiSeq2000 at the Duke Sequencing Core.

The miRNA sequencing reads were obtained in fastq format and pre-processed to remove the Illumina adapter sequences and any low-quality reads using scripts from the fastx toolkit (http://hannonlab.cshl.edu/fastx_toolkit/). On average, ~10 million reads were obtained per library. To identify miRNAs, reads were first aligned to the human (HG19) and EBV genomes and annotated according to mirbase v21 (<http://www.mirbase.org/>) using miRDeep2 modules (25). Read counts for each miRNA were determined using the quantifier module of miRDeep2. To identify differentially expressed (DE) miRNAs, miRNA read counts were analysed by edgeR using trimmed mean of M-values (TMM) for normalization (26, 27) (Fig 2 and Tables S1-S3). We required a minimum of 40 reads per mature miRNA in at least one of the ten libraries to be included in the edgeR analysis. DE miRNAs with a LogFC p value < 0.05 are reported in Tables S2 (deleted EBER1 versus wt and EBER1 revertant) and S3 (deleted EBER2 versus wt and EBER2 revertant).

Quantitative PCR analysis of cellular miRNAs

Small RNA was isolated with the miRVana miRNA Isolation Kit (Life Technologies) from up to 6 different LCLs representing each of the EBER expression status. Real-time quantitative RT-PCR analysis was performed with TaqMan MicroRNA Reverse Transcription Kit (Applied

Biosystems; AB) and TaqMan miRNA Assays (AB) according to manufacturer's instructions using a ViiA7 qPCR machine (Applied Biosystems). The following TaqMan miRNA Assays were used: miR-340-5p (hsa-miR-340; RT 002258) and miR-340-3p (hsa-miR-340*; RT 002259). Threshold cycle (C_T) values were normalized to RNU48 (RT 001006) and expressed as values relative to the wild-type samples. Each cDNA sample was analysed in triplicate.

Q-PCR for LMP RNAs

Total RNA was isolated with TRIzol (Invitrogen), cytoplasmic RNA was isolated with the RNeasy Mini Kit (QIAGEN) and cDNA was prepared using the ProtoScript First Strand cDNA Synthesis Kit (New England BioLabs). FastStart Universal SYBR Green Master (ROX) mix was used for Q-PCR with primer sequences as described (17). The comparative C_T method (28) was used for relative quantification.

Humanised mice

Newborn HLA-A*0201 transgenic NOD/LtSz-Scid IL2R γ null (NSG-A2tg) mice were irradiated and injected intrahepatically with CD34⁺ human hematopoietic progenitor cells as described previously (29). The reconstitution of human immune system components in the peripheral blood was analysed prior to the beginning of experiments (normally 12 weeks after engraftment). Mice were then injected with 10⁵ green Raji units of EBV, either wild type, EBER mutant or revertant. Samples were taken at weekly time intervals of the blood, starting 2 weeks after infection, and of the spleen at time of sacrifice 4 weeks after infection for determination of virus DNA load and for flow cytometric analysis.

Flow Cytometry

The composition of blood and spleen samples from the humanised mice was analysed using anti-human CD45 (HI30, Biolegend), anti-CD3 (UCHT1, Biolegend), anti-CD4 (RPA T4, Biolegend), anti-CD8 (SK1, Biolegend), anti-HLA-DR (L243, Biolegend), anti-CD45RO (UCHL1, BD Pharmingen) and anti-CD19 (HIB19, BD Pharmingen). Spleens were mechanically disrupted and filtered through a 70µm cell strainer. Erythrocyte lysis in whole blood or in spleen suspensions was done using NH₄Cl. Cell suspensions were stained with the indicated antibodies for 15min, 4°C and washed. Statistical analysis for all mouse experiments used two tailed T-tests. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Binding of EBER1 to RPL22 is confirmed in LCLs but no effect of EBER1 was detected on p53 related cell responses or protein level.

First we confirmed the binding of RPL22 to endogenous EBER1 in extracts of an LCL, comparing with the known binding in 293 cells of EBER1 to RPL22, where both were expressed from transfected plasmids. Specific pull down with an anti-FLAG antibody of EBER1 but not EBER2 was observed in cells expressing a Flag tagged RPL22 protein (Fig 1A, B). Although mRNA for p53 was not one of those we previously found to correlate with EBER expression in LCLs (11), the RPL22 effect on p53 is thought to be at the level of translation (22). Thus, p53 protein level was tested by Western blotting in a panel of LCLs made with recombinant EBV with or without EBER1 expression. The response to cisplatin treatment, which causes p53 stabilisation was also tested. There was no significant difference in the p53 levels or responses between the cells with or without EBER1 expression (Fig 1C).

Effect of EBERs on cellular miRNAs

We have previously reported on a set of differentially expressed mRNAs in the absence of EBER1 or EBER2 (11). To determine whether EBER RNAs might have an effect on the levels of cellular miRNAs, small RNAs were isolated from LCLs containing either wild type B95-8 BAC EBV or EBER deletion mutants of EBV and analysed by deep sequencing. Appropriate expression of the EBER1 and EBER2 RNAs was confirmed in the cell lines by Northern blotting (Fig 2A). Small RNA deep sequencing libraries were generated and sequencing reads were processed as described previously (24). We detected miRNAs expressed from all 8 EBV pre-miRNAs and 491 mature human cellular miRNAs. The general pattern of viral and cellular miRNA expression (Fig 2B) was similar to that observed previously in EBV B95-8 LCLs (24). In accordance with previous LCL miRNA sequencing studies (24, 30), we found no evidence for production of discrete miRNA-like products from the EBER RNAs.

To identify differentially expressed miRNAs in EBER knockout LCLs compared to wild-type or revertant LCLs, we analysed miRNA read counts using edgeR (27). miRNA read counts are reported in Table S1 and significantly expressed miRNAs are summarized in Tables S2, S3, and Fig 2C. We identified sixteen miRNAs ($p\text{-value} < 0.01$ and $-2 > \log FC > 2$) with altered expression levels in response to the deletion of EBER1. Notably, we observed significant differences in the levels of miR-340-3p, miR-340-5p, miR-190a-3p, miR-190a-5p, and miR-33a-5p in response to deletion of EBER1 (Fig. 2C-E, Table S2). Only small changes in miRNA expression levels (such as miR-199a) were observed in response to deletion of EBER2 (Fig. 2C, Table S1 and S3).

To further test the significance of the miRNA expression differences indicated by the sequencing results, Taqman quantitative RT-PCR assays were implemented for two of the

miRNAs showing the largest fold changes in expression (miR-340-5p and -3p) in response to EBER1 deletion. To counter random effects of clonal variation, RNA from 6 independently established LCLs for each EBER1 deletion mutant, wild type or revertant was used and each was assayed in triplicate. In this assay, the expression of both miR-340-5p and -3p correlated with EBER1 expression (Fig 2F). Since the levels of these miRNAs are quite low (Fig 2D, Table S1) in LCLs, our overall conclusion is that it seems unlikely that the main function of EBERs in LCLs is to alter levels of cellular miRNAs. This does not exclude a greater effect in a different stage of infection or a different cell type.

Deletion of EBER1 or EBER2 correlates with raised level of LMP2 RNAs in LCLs

Recent studies reported a new mechanism by which EBER2 could associate with PAX5 and help to target PAX5 to a DNA binding site within the terminal repeat region of the EBV genome, affecting expression of LMP1 and LMP2 (17). Those studies used BJAB cells containing P3HR1 EBV (BJAB-B1 cells) and EBER2 level was knocked down with siRNA (17). An antisense oligonucleotide to EBER2 was found to cause a 50% increase in LMP1 and LMP2 RNA levels when transfected into a BJAB cell line containing B95-8 EBV, indicating that EBER2 caused a reduction in the levels of these RNAs (17). Using qPCR with the same primers on cytoplasmic RNA, we did not observe any significant difference in the level of LMP1 RNA between the EBER2 deletion LCLs or wild type EBV LCLs but LMP2A and LMP2B RNA levels were 2-3 fold higher when either EBER1 or EBER2 was deleted (Fig 3), particularly when the cDNA synthesis was primed with oligo-dT (Fig 3B).

Infection of mice with a human haematopoietic system with EBV lacking EBER genes

219 Seeing small effects of deletion of EBER RNAs in LCLs, we tested whether EBERs would affect
220 the ability to establish EBV infection in NSG mice with a humanised haematopoietic system.
221 These mice currently provide the best opportunity to investigate the physiological effects of
222 EBV genes on infection and the immune response (31).

223 EBV was produced from 293 cell lines containing BAC B95-8 EBV, either wild type, EBER1
224 deleted, EBER2 deleted, EBER2 revertant (EBER2 reintroduced into the EBER2 deficient
225 virus) or both EBERs deleted (EBERKO). Groups of mice were infected with 10^5 infectious
226 units of virus and monitored over a 4-8 week period in three experiments, each using
227 different groups of reconstituted mice.

228 In the three separate mouse experiments involving a total of 44 correctly reconstituted
229 mice, the proportion of mice that became infected varied between experiments but overall
230 there was no significant difference in the frequency of infection detected in the blood or the
231 spleen caused by deletion of either or both EBER genes from the virus genome. Spleen and
232 blood viral loads for the all three independent experiments are shown in Fig 4A. There are
233 infected animals with each EBV strain but also some mice in which infection has not been
234 successful.

235 In addition we analysed parameters of cell mediated immune responses towards the
236 different viral infections. We observed a tendency towards more pronounced $CD8^+$ T cell
237 expansion in the infection with EBER1 deficient viruses (Fig 4B). However, this tendency was
238 primarily observed in one experiment and was not present in infections with an EBV virus
239 deficient in both EBERs. These experiments demonstrate that it will be feasible to use this
240 mouse system for in vivo investigation of EBER biology.

241

242 **DISCUSSION**

243 Since EBERs are expressed abundantly in latent EBV infections but at lower levels in the lytic
244 cycle, it seems most likely that their functions will be related to latent infection, evasion of
245 immune surveillance or ensuring that the latent EBV genome can be reactivated when it is
246 due for replication. However, the many reports of functions for the EBER RNAs have still not
247 resulted in a clear understanding of their mechanisms of action. It has been proposed that
248 EBER RNAs are present in the EBV particle and function to induce an interferon response
249 (32) which can aid B cell growth but another report found that highly purified EBV virions
250 contain only 0.003 EBER transcripts per virion (33), casting doubt on the significance of
251 EBERs in the virion.

252 It is certainly possible that the main effects of EBERs are at a different stage of infection or
253 in a cell type that we have not assayed but we have focused on EBER effects in LCLs. The
254 small changes in cellular miRNA expression may contribute to some of the effects we
255 reported previously on cell mRNA levels in LCLs according to EBER expression (11).

256 Our sequencing results corroborate previous observations regarding miR-190 expression in
257 EBV-infected, EBER-expressing cells. Of note, the miR-190a promoter has been recently
258 shown to be responsive to the presence of EBER RNAs and ectopic expression of EBER1, in
259 particular, resulted in enhance levels of miR-190 in EBV-negative Burkitt's lymphoma cells
260 (34).

261 Our results provide some support for the recent report that EBER2 tends to reduce the level
262 of LMP2 RNA (17). In that study an antisense EBER2 oligonucleotide was used to reduce the

263 level of EBER2 and caused about a 2 fold increase in LMP2 RNA. There is always a risk of off
264 target effects with antisense oligonucleotides and it is notable that the antisense EBER2
265 oligonucleotide that was used has an 18/18 perfect match (GAGCATTTGCAAGTCAGG) to an
266 intron sequence in the human SLC4A8 bicarbonate transporter, which is expressed in
267 lymphocytes and can determine cell intracellular pH. However, our results using EBER
268 deletion mutants are partly consistent. In our study, deletion of either EBER1 or EBER2
269 results in an increased level of LMP2 cytoplasmic RNA. We do not know whether the specific
270 binding of EBER2 to PAX5 and association with the terminal repeat sequence is relevant to
271 the LMP2 RNA effect since we saw an increase in LMP2 RNA when either EBER1 or EBER2
272 was deleted. The focus of the previous study on EBER2 meant that an effect of EBER1
273 deletion on LMP2 RNA levels was not tested in those experiments (17).

274 One clear feature of our experiments is that we have used B95-8 BAC EBV whereas many
275 other studies have used either P3HR1 or Akata EBV. Now there is a wider appreciation of
276 the variation of EBV strains (35) it may be possible to use more wild type EBV strains to
277 identify functions for the EBERs. It seems most likely that the true physiological phenotypes
278 for the EBERs may be revealed in an in vivo infection challenged by a normal immune
279 response. This may be observed in the infection of humanised mice and we have now
280 shown that deletion of EBERs does not prevent infection of the mice, which should make
281 this type of analysis possible. There is a significant variability in the kinetics of infection
282 between individual mice and this means that larger numbers of animals will most likely be
283 required, but we have already observed a small effect on the T cell expansion. So far these
284 in vivo results suggest that CD8⁺ T cell expansion may be attenuated by EBER1, which would
285 be consistent with an immune regulatory potential of EBERs, possibly via innate immune

detection of these viral molecular patterns (12). Differential innate immune activation by EBER positive and negative viruses should, therefore, be studied in more detail in future studies. Our experiments show that humanised mice will be a viable system for investigation of EBER function in vivo.

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Figure legends

Figure 1

A) Flag tagged RPL22 or a negative control protein (Flag tagged Schlafen) were co-expressed with EBER1 or EBER2 by transient transfection in 293 cells. Cell extracts were incubated with anti-FLAG antibody bound to protein G sepharose beads. RNA was extracted from the beads (IP) and the unbound supernatant (Sup) and tested for EBER RNA by Northern blotting.

B) Flag tagged RPL22 or negative control protein (Flag tagged Schlafen) were expressed by Neon transfection in an LCL containing B95-8 BAC EBV. Cell extracts were tested for binding to EBERs as in part A.

C) Three independent Δ EBER1 LCLs (light grey bars) or wt EBV LCLs (black bars) were treated with 20ug/ml cisplatin in triplicate. The number of viable cells (excluding trypan blue) was quantified before (0h) or after 16h of cisplatin treatment and p53 protein was detected by western blotting cell extracts made at the same time points. Actin was used as loading control on the western blots.

Figure 2

A) EBER1 and EBER2 expression in the wt and EBER-deleted LCLs used for deep sequencing analysis was confirmed by Northern blotting (11). 0.5 ug of total RNA was used per well.

B) Distribution of most abundant cell and EBV miRNAs in the EBV LCLs studied. Analysis was restricted to miRNAs showing 40 or more read counts in 6 wild type/revertant samples and a coefficient of variation less than 1 in more than half the samples.

- C) Summary of fold changes (logFC) of cellular miRNAs showing significant changes correlating with EBER1 or EBER2 expression as determined by deep sequencing and edgeR analysis.
- D) Normalized miRNA reads counts for miR-190a and miR-340 in EBER1-deleted (delE1) LCLs compared to wild-type (wt) and EBER1 revertant (E1R) LCLs. "A" and "B" denote the two individual LCLs analysed for each condition.
- E) Normalized miRNA read counts for miR-33a in EBER1-deleted LCLs.
- F) Summary of fold changes for miR-340 expression using Taqman qRT-PCR assays. The expression levels of miRNAs were normalized to RNU48. The values represent means \pm SE of 6 independent samples per EBV type (5 in the case of EBER1 revertants). The wild-type expression levels were set to 1 for each miRNA, whereas the levels of other samples were expressed relative to the wild type. Each cDNA sample was analysed in triplicate.

Figure 3

Cytoplasmic RNA from two LCLs each for EBV wild type, deletion of EBER1, revertant, deletion of EBER2 or revertant was used for cDNA synthesis using either (A) random primers or (B) oligo dT. Q-PCR with the same primers as in (17) was then used in duplicate assays to measure the levels of RNA for LMP1, LMP2A and LMP2B, using GAPDH as a reference. The $2^{-\Delta\Delta CT}$ method of comparative PCR (28) was used to analyse the results.

Figure 4

A) Humanized NSG-A2tg mice with EBV EBER mutants show persistent infection 4 weeks after injection as measured by EBV DNA load. EBV viral loads were quantified in spleen and whole blood four weeks after infection for wild-type (EBV wt), EBER1 deficient (E Δ 1), EBER2 deficient (E Δ 2), EBER1 and 2 deficient (E Δ 12) and EBER2 revertant (E2rev) viruses.

B) CD8⁺ T cell expansion is slightly elevated in the absence of EBER1. CD8⁺ to CD4⁺ T cell ratio was assessed by flow cytometry after four weeks of infection with the same viruses as in A.

SUPPLEMENTARY TABLES

Table S1

miRNA sequencing results. Reported are the raw read counts for each mature miRNA as annotated in mirbase v21.

Table S2

Differentially expressed miRNAs in EBER1 deleted LCLs compared to wild-type and EBER1 revertant LCLs expressed as fold change (FC) as determined by edgeR.

Table S3

Differentially expressed miRNAs in EBER2 deleted LCLs compared to wild-type and EBER2 revertant LCLs expressed as fold change (FC) as determined by edgeR.

Figure 1

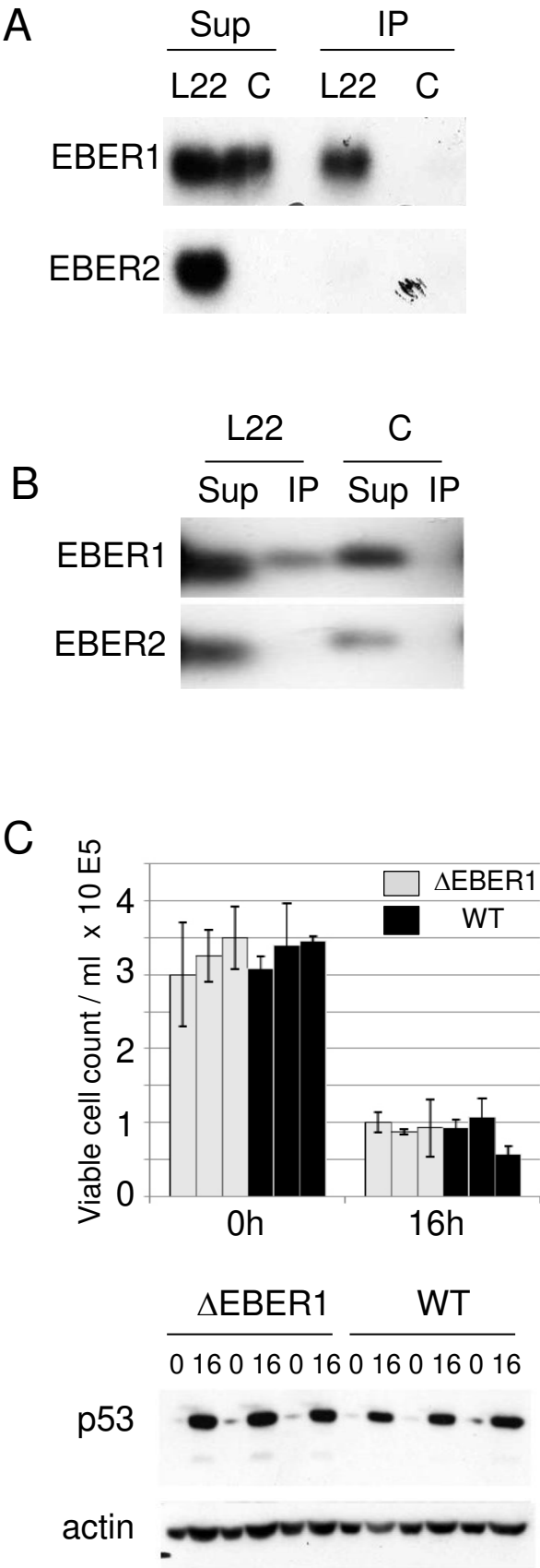


Figure 2

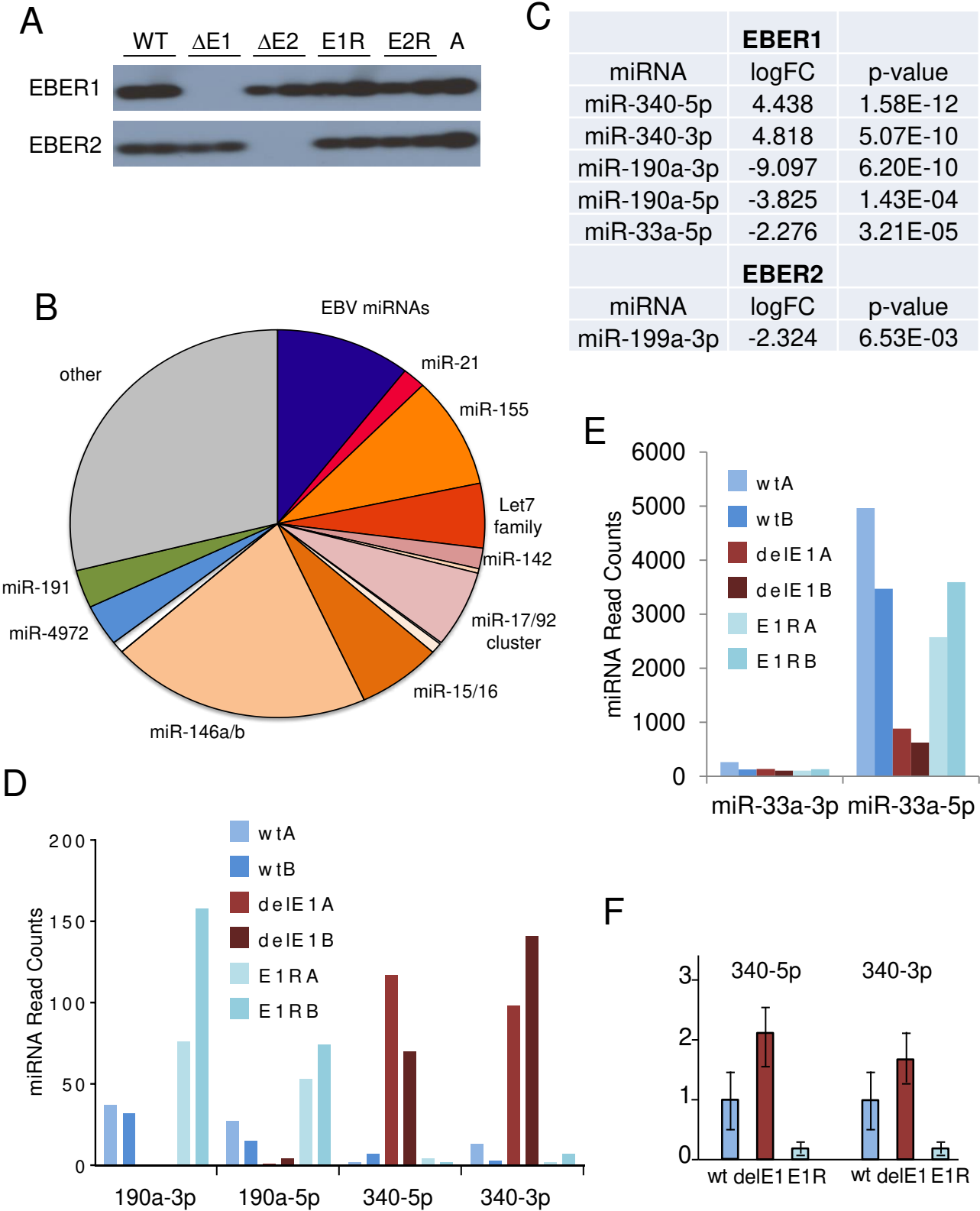
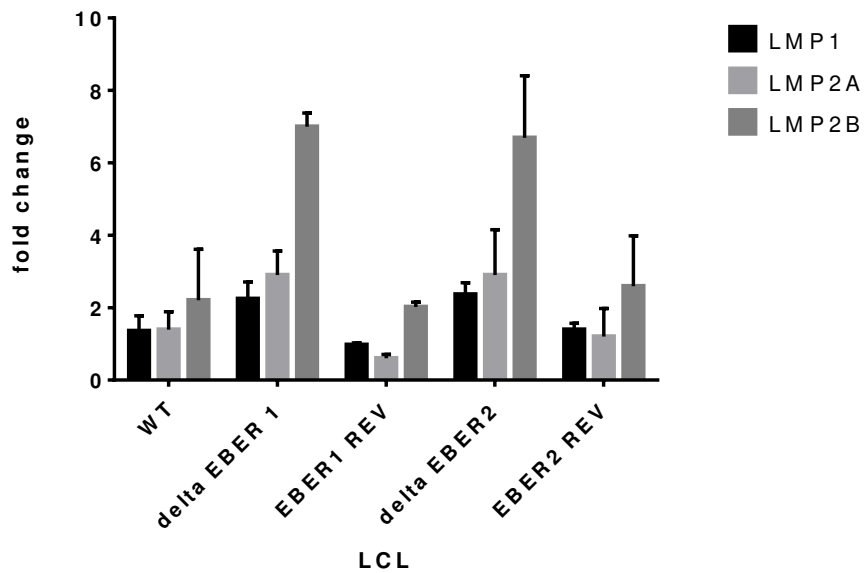


Figure 3

A

Q-PCR on EBER deletion LCL
(cytoplasmic RNA - random primer)



B

Q-PCR on EBER deletion LCL
(cytoplasmic RNA - oligo dT)

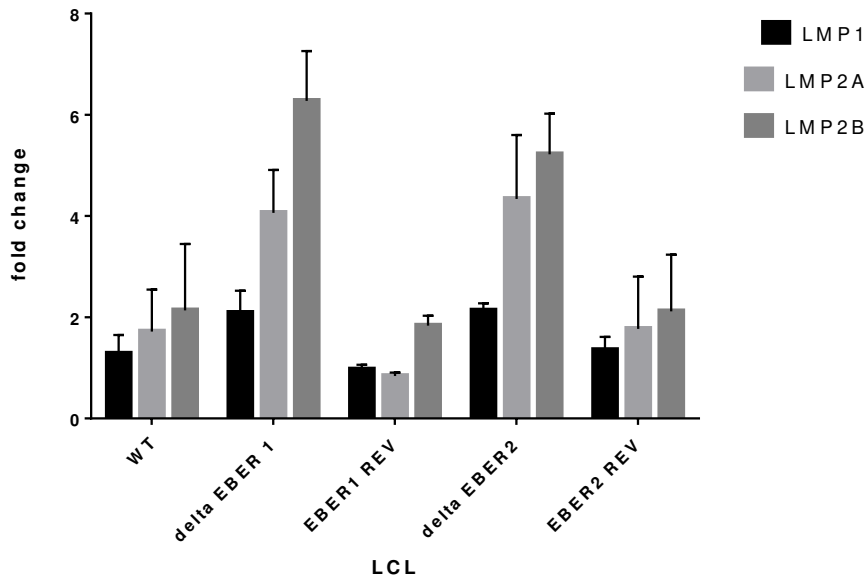
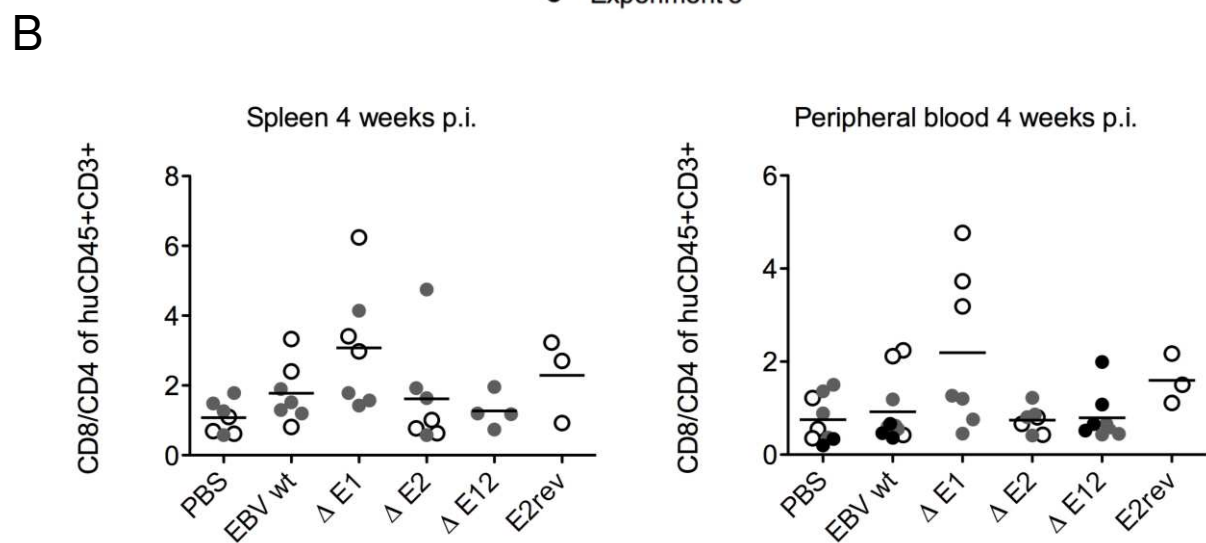
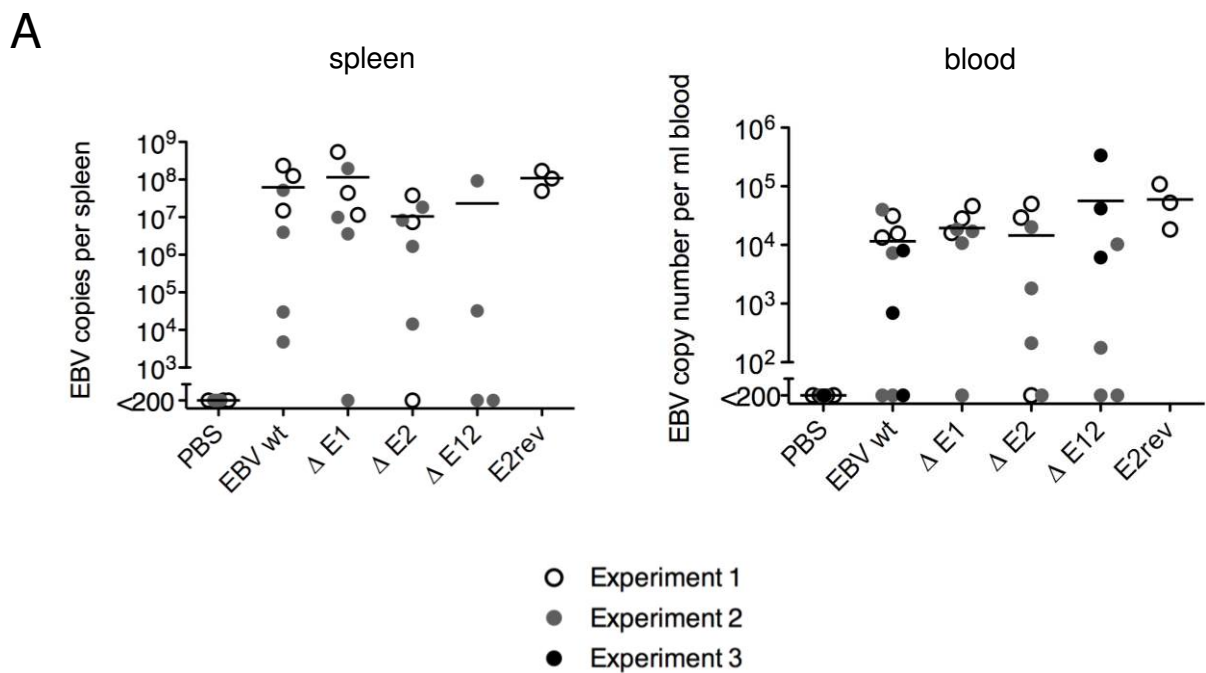


Figure 4



miRNA	wtA	wtB	delE1A	delE1B	delE2A	delE2B	E1RA	E1RB	E2RA	E2RB
ebv-miR-BART1-3p	7501	7298	10095	5571	8241	12102	8306	12262	10496	3889
ebv-miR-BART1-5p	25713	37940	38986	49882	32961	49358	56383	67827	29848	14152
ebv-miR-BART15	17862	12975	12538	6264	11435	19053	9777	19937	15615	5864
ebv-miR-BART2-3p	394	375	425	605	311	958	675	884	603	411
ebv-miR-BART2-5p	9847	10386	8659	14440	7214	24397	20521	24995	13949	7361
ebv-miR-BART3-3p	9967	6504	13052	18154	7986	12947	12189	20931	11371	7035
ebv-miR-BART3-5p	5638	4418	5423	5917	5964	10816	6452	7228	6682	2174
ebv-miR-BART4-3p	2168	1865	2357	2235	2071	3174	2308	3120	2491	700
ebv-miR-BART4-5p	48575	38448	85716	39404	45199	65867	36698	42528	46400	16713
ebv-miR-BHRF1-1	287511	181966	172519	361556	88261	241954	150580	209495	245004	76590
ebv-miR-BHRF1-2-3p	54843	29884	27105	43340	14805	45228	23271	36451	44434	11659
ebv-miR-BHRF1-2-5p	1518	635	384	854	495	1433	495	775	1311	263
ebv-miR-BHRF1-3	485841	442158	351890	262920	258565	553569	453926	582149	507809	172421
hsa-let-7a-3p	1419	1059	737	1028	862	2078	972	1542	1236	657
hsa-let-7a-5p	34372	46894	29515	46539	26554	39648	35601	60244	17718	8527
hsa-let-7b-3p	30	84	135	92	200	25	22	45	198	75
hsa-let-7b-5p	187	405	362	912	2108	178	388	355	475	174
hsa-let-7c-5p	821	501	540	507	436	846	661	658	485	222
hsa-let-7d-3p	1073	1364	1238	1345	1086	2206	1349	1169	822	314
hsa-let-7d-5p	15829	13911	10604	17180	7590	17392	9668	17034	7870	5120
hsa-let-7e-5p	151	329	148	355	145	170	235	286	89	32
hsa-let-7f-1-3p	671	725	632	361	785	1644	522	794	859	349
hsa-let-7f-2-3p	282	193	150	195	165	456	263	371	310	150
hsa-let-7f-5p	163792	124940	110442	156648	94960	193181	139088	204609	137086	75024
hsa-let-7g-3p	606	423	376	461	344	949	458	748	821	554
hsa-let-7g-5p	23288	26899	15795	37045	14931	28397	20298	49017	18440	13016
hsa-let-7i-3p	736	738	593	920	473	1169	1105	1953	1032	761
hsa-let-7i-5p	36364	33255	20244	42422	20966	49234	31533	60818	31360	17552
hsa-miR-101-3p	2175	1157	975	1759	1130	2788	1344	3489	2331	1563
hsa-miR-103a-2-5p	468	358	288	78	246	483	281	490	416	296
hsa-miR-103a-3p	16690	10499	9786	16902	8442	20285	11364	19693	14555	9008
hsa-miR-106a-3p	33	37	1	33	10	11	27	41	17	7
hsa-miR-106a-5p	1192	1156	114	1001	454	717	968	915	270	149
hsa-miR-106b-3p	3740	3685	2293	5109	2544	5152	3192	5062	4354	1522
hsa-miR-106b-5p	4836	2545	2171	4630	2143	6029	2410	4219	3961	1922
hsa-miR-107	4279	2907	2091	5652	1685	4675	3820	7035	3741	2952
hsa-miR-10a-3p	230	188	46	211	31	27	110	269	95	4
hsa-miR-10a-5p	67338	66323	19822	74241	12831	7226	61139	118785	33488	1867
hsa-miR-10b-5p	54	464	18	95	8	5	343	308	30	9
hsa-miR-1180-3p	947	906	1003	611	556	811	720	517	658	307
hsa-miR-1246	742	695	354	1322	221	593	960	2651	270	361
hsa-miR-1249-3p	41	18	14	34	41	39	15	24	12	4
hsa-miR-1254	58	39	49	77	29	94	58	97	58	38
hsa-miR-1255a	59	21	38	54	29	79	34	34	37	31
hsa-miR-125a-3p	9	19	14	17	2	1	44	6	4	1
hsa-miR-125a-5p	652	2441	1570	1199	514	152	2475	744	497	173
hsa-miR-125b-2-3p	5	7	14	45	10	109	46	44	37	4
hsa-miR-125b-5p	57	159	331	234	304	1529	958	1119	735	79
hsa-miR-126-3p	67	23	22	16	17	58	21	19	34	12
hsa-miR-126-5p	156	55	38	46	35	139	42	42	71	20
hsa-miR-1260a	14459	8231	11454	9756	12019	14940	5228	6957	8548	5075
hsa-miR-1260b	17672	10432	14294	11626	13849	18637	6158	8678	10931	6438
hsa-miR-1261	165	123	149	116	121	248	128	224	161	198
hsa-miR-1268a	194	376	56	233	386	220	396	339	289	141
hsa-miR-1268b	195	379	56	234	387	221	398	340	296	141
hsa-miR-127-3p	10	230	7	363	4	3	159	126	6	0

hsa-miR-1271-5p	816	1015	894	158	702	975	715	1025	902	562
hsa-miR-1273g-3p	31	43	27	27	24	43	80	67	42	31
hsa-miR-1273h-3p	254	330	299	401	227	536	234	273	371	198
hsa-miR-1273h-5p	29	64	57	65	50	92	39	54	64	33
hsa-miR-1275	85	259	90	315	342	381	596	250	146	63
hsa-miR-1277-5p	22	27	7	27	35	68	34	69	32	18
hsa-miR-128-1-5p	220	207	178	303	121	336	110	220	322	117
hsa-miR-128-3p	6935	4843	4769	7030	3608	7905	3757	7021	5468	2825
hsa-miR-1285-3p	237	197	184	265	162	392	174	287	265	123
hsa-miR-1285-5p	42	64	50	65	42	72	40	80	58	40
hsa-miR-1287-5p	25	12	24	9	24	36	9	18	63	18
hsa-miR-1290	864	742	396	770	453	840	1175	2436	539	402
hsa-miR-1292-5p	170	153	239	231	165	281	157	182	209	119
hsa-miR-1294	45	27	26	19	28	82	34	41	34	10
hsa-miR-1296-5p	173	137	142	118	95	272	97	167	213	59
hsa-miR-1299	1008	72	2	113	186	10	16	33	617	5
hsa-miR-1301-3p	403	227	382	420	248	681	319	403	268	151
hsa-miR-1303	1531	1050	729	1532	931	2707	1154	1725	3066	757
hsa-miR-1304-3p	305	233	213	174	222	541	120	161	263	96
hsa-miR-1307-3p	745	635	593	952	520	1291	581	916	766	318
hsa-miR-1307-5p	12239	5193	8653	12890	6168	17652	6875	12494	14285	10003
hsa-miR-130a-3p	5155	1236	1283	1074	1075	1986	713	1620	2633	884
hsa-miR-130b-3p	6479	4886	4671	6801	4767	10797	3410	5657	5259	2148
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hsa-miR-132-3p	1585	886	1576	1109	844	1625	335	360	607	485
hsa-miR-132-5p	595	266	445	312	303	497	111	138	254	197
hsa-miR-135b-5p	44	2	5	15	52	0	66	148	17	11
hsa-miR-138-1-3p	258	450	1306	879	922	1167	757	996	643	343
hsa-miR-138-5p	3547	2980	9660	10783	9473	13124	9060	15039	14798	9417
hsa-miR-140-3p	5479	3677	3553	6688	3424	7291	4357	7887	5689	3139
hsa-miR-140-5p	285	180	173	263	246	406	212	359	311	124
hsa-miR-141-3p	1397	1277	709	2337	1075	1641	2148	3895	1942	1700
hsa-miR-142-3p	18703	11569	5918	17527	14887	32821	15758	26665	19684	12283
hsa-miR-142-5p	107861	71338	52781	124810	81209	181428	105070	162707	129927	81561
hsa-miR-143-3p	394	431	1085	906	331	354	5466	3247	1388	3947
hsa-miR-145-5p	13	17	63	16	14	14	182	132	72	158
hsa-miR-1468-5p	67	75	116	91	87	100	106	121	52	36
hsa-miR-146a-3p	2712	1250	1863	1535	970	3347	2030	3261	2394	1644
hsa-miR-146a-5p	1505959	819903	1489927	1392840	770399	1778532	1807465	2048171	1282441	1004313
hsa-miR-146b-3p	409	352	241	221	129	311	225	172	500	456
hsa-miR-146b-5p	143389	108672	106616	99481	68008	109450	93947	74922	125402	124132
hsa-miR-148a-3p	51731	62089	32893	48887	48499	108270	91155	112444	50482	39677
hsa-miR-148a-5p	4118	5114	3294	4613	3154	9405	5559	9208	4575	4397
hsa-miR-148b-3p	1406	2064	2095	2352	2194	4298	1674	3468	1710	921
hsa-miR-148b-5p	901	644	637	950	566	1746	611	1181	992	589
hsa-miR-150-5p	1337	1526	1674	1623	2151	1564	1069	1792	2036	451
hsa-miR-151a-3p	816	1194	1468	1361	1234	1105	466	325	1561	91
hsa-miR-151a-5p	9504	13575	26393	20531	15951	12240	5892	3758	16283	1368
hsa-miR-151b	474	615	1243	1516	784	507	555	329	914	104
hsa-miR-152-3p	253	282	168	284	212	285	281	182	216	63
hsa-miR-152-5p	30	28	22	23	21	44	24	21	30	4
hsa-miR-155-3p	4205	3868	2749	3797	2046	5217	3257	6716	7427	4450
hsa-miR-155-5p	583661	589723	525293	874474	392760	814807	841460	1177736	589240	467170
hsa-miR-15a-3p	629	595	402	286	467	840	492	850	896	531
hsa-miR-15a-5p	5402	3108	3312	6634	3236	6765	3967	7373	6122	3778
hsa-miR-15b-3p	1240	704	495	1168	630	1148	529	895	902	311

hsa-miR-15b-5p	15143	11195	15997	16345	14028	23550	8469	9583	10471	4688
hsa-miR-16-1-3p	35	25	7	30	22	36	44	61	41	35
hsa-miR-16-2-3p	4715	3646	2726	5908	2303	4982	4554	6245	5016	3611
hsa-miR-16-5p	275936	187358	217586	355577	222430	365336	240051	287678	266462	172955
hsa-miR-17-3p	4212	2524	2340	3929	1707	4230	1715	3342	3936	2787
hsa-miR-17-5p	8476	9401	5159	8299	8866	14375	7175	8243	7398	2967
hsa-miR-181a-2-3p	3911	3451	3306	3688	3013	6016	3741	5481	5187	432
hsa-miR-181a-3p	1511	1740	598	1439	399	380	1328	2941	569	242
hsa-miR-181a-5p	92330	156155	64437	202047	46037	73502	188440	346702	86576	20790
hsa-miR-181b-2-3p	51	31	16	38	23	50	31	64	56	5
hsa-miR-181b-3p	298	240	51	170	57	45	125	313	70	28
hsa-miR-181b-5p	22463	24517	10649	31589	9376	19585	24667	47670	17298	2714
hsa-miR-181c-3p	225	510	608	569	179	442	778	1339	219	284
hsa-miR-181c-5p	1521	3015	2373	4788	814	2100	4701	10081	1273	1935
hsa-miR-181d-5p	137	368	196	385	107	244	505	881	98	127
hsa-miR-182-5p	602	573	223	1033	550	256	654	898	622	437
hsa-miR-183-5p	318	286	123	529	208	123	286	478	263	165
hsa-miR-184	9	11	7	13	7	10	77	80	12	18
hsa-miR-185-3p	51	33	36	60	45	86	22	75	55	54
hsa-miR-185-5p	5653	3191	3142	5802	3339	6901	3216	5940	5027	3405
hsa-miR-186-3p	600	398	226	246	324	995	299	605	703	494
hsa-miR-186-5p	52650	36142	48565	73043	40478	85928	46672	73495	43800	28965
hsa-miR-188-3p	197	199	275	120	248	310	195	261	188	88
hsa-miR-188-5p	245	196	97	72	149	251	140	284	230	61
hsa-miR-18a-3p	760	810	462	860	476	884	380	574	649	299
hsa-miR-18a-5p	1380	1014	621	1375	817	1809	730	1235	1229	558
hsa-miR-18b-5p	92	51	8	80	18	45	54	93	18	8
hsa-miR-1908-5p	96	107	87	121	130	269	75	71	106	26
hsa-miR-190a-3p	37	32	0	0	6	16	76	158	3	9
hsa-miR-190a-5p	27	15	1	4	1	2	53	74	1	6
hsa-miR-191-3p	310	237	377	222	235	493	188	213	285	109
hsa-miR-191-5p	249662	246023	452628	267461	372907	466871	253385	331994	214994	147632
hsa-miR-192-3p	24	130	15	58	9	9	42	66	10	9
hsa-miR-192-5p	3972	24372	1616	25362	1704	2249	10106	12396	2275	1440
hsa-miR-193b-3p	3616	5460	4492	10162	4176	10147	6159	11393	6005	3234
hsa-miR-193b-5p	50	124	42	83	125	134	108	131	44	23
hsa-miR-194-5p	64	375	22	431	44	52	158	212	32	27
hsa-miR-195-5p	203	179	180	185	148	258	186	192	237	154
hsa-miR-196a-5p	314	96	2	219	7	2	129	258	9	4
hsa-miR-196b-5p	93	19	0	104	875	22	1	3	29	0
hsa-miR-197-3p	827	794	918	672	788	1144	450	595	539	251
hsa-miR-199a-3p	26	48	18	30	5	19	52	94	46	49
hsa-miR-199a-5p	45	138	72	44	35	88	138	231	135	87
hsa-miR-199b-3p	26	48	18	30	5	19	52	94	46	49
hsa-miR-199b-5p	43	31	23	6	9	25	26	18	17	3
hsa-miR-19a-3p	13366	9629	3717	9662	6122	15781	10995	25228	16218	9278
hsa-miR-19a-5p	113	76	22	107	46	125	36	111	161	68
hsa-miR-19b-1-5p	27	36	26	34	18	58	24	40	75	52
hsa-miR-19b-3p	47293	36196	23060	32763	20312	50501	38916	81904	52909	37285
hsa-miR-200a-3p	52	57	20	74	27	43	82	121	69	49
hsa-miR-200b-3p	61	68	59	45	41	75	60	79	87	27
hsa-miR-200c-3p	676	497	488	788	421	809	523	828	688	377
hsa-miR-204-5p	8	66	4	26	3	1	97	64	4	3
hsa-miR-205-3p	0	1	0	3	0	0	18	61	0	0
hsa-miR-205-5p	407	2908	270	2312	76	16	34040	84727	71	100
hsa-miR-208b-3p	12	20	8	29	13	1	20	47	63	31

hsa-miR-20a-3p	36	37	31	38	23	43	29	58	65	36
hsa-miR-20a-5p	12481	15217	6842	11701	10278	19091	10763	14424	13347	6061
hsa-miR-20b-3p	97	89	7	75	30	47	55	52	27	9
hsa-miR-20b-5p	777	962	44	860	364	468	842	815	168	69
hsa-miR-21-3p	23254	21814	11872	29128	10455	27009	21495	44798	19796	19788
hsa-miR-21-5p	99400	104062	42749	104764	57767	139144	110786	243630	87386	61353
hsa-miR-210-3p	2563	1696	988	1594	1320	2970	2230	1684	2328	1009
hsa-miR-210-5p	251	140	252	139	173	367	197	110	181	108
hsa-miR-2110	144	137	244	214	155	222	119	149	130	79
hsa-miR-2116-3p	130	102	127	71	92	216	71	118	136	70
hsa-miR-2116-5p	60	36	63	36	47	81	40	31	49	32
hsa-miR-212-3p	273	148	281	193	134	266	35	45	77	46
hsa-miR-212-5p	140	62	228	67	104	87	18	17	36	22
hsa-miR-215-5p	20	83	17	112	20	19	93	139	13	17
hsa-miR-22-3p	39076	44495	70141	100515	58202	113237	92340	161446	100524	87988
hsa-miR-22-5p	152	141	204	526	128	293	414	848	374	490
hsa-miR-221-3p	3303	2941	2003	5301	673	5514	8430	14318	2529	11183
hsa-miR-221-5p	585	486	474	491	118	814	1376	1945	444	2488
hsa-miR-222-3p	11636	8907	11537	11205	3049	21782	19114	21729	8461	26755
hsa-miR-222-5p	95	43	62	54	26	121	71	74	66	214
hsa-miR-223-3p	615	185	232	229	256	581	145	98	416	114
hsa-miR-223-5p	68	28	20	25	32	53	20	8	34	2
hsa-miR-2277-5p	50	24	42	46	29	68	37	28	33	13
hsa-miR-23a-3p	13846	9823	11357	11381	11250	19846	20328	25688	8783	9718
hsa-miR-23b-3p	4163	3578	4198	3572	4169	6025	6128	8210	5573	3263
hsa-miR-24-1-5p	114	107	116	28	147	132	139	199	195	92
hsa-miR-24-2-5p	644	453	557	546	737	1110	785	927	520	512
hsa-miR-24-3p	20115	12856	17617	18492	17107	29196	26014	30943	18279	14945
hsa-miR-2467-5p	41	23	18	36	21	64	22	33	42	10
hsa-miR-25-3p	15377	14660	7549	17966	10764	19420	13136	20822	12437	4593
hsa-miR-25-5p	1201	1287	957	1457	845	1854	639	920	1297	374
hsa-miR-26a-2-3p	89	68	71	48	45	82	26	61	75	20
hsa-miR-26a-5p	196549	158978	201674	237889	207255	250450	172901	270161	193940	81244
hsa-miR-26b-3p	1671	1429	1452	1209	1376	2089	1354	1449	1454	518
hsa-miR-26b-5p	9265	8664	5227	13681	7864	12569	11574	18557	8314	3868
hsa-miR-27a-3p	42313	31802	35162	37426	40777	68996	57736	70915	38747	37572
hsa-miR-27a-5p	84	106	40	128	72	148	178	195	102	63
hsa-miR-27b-3p	45338	42156	40658	41662	45481	62660	56267	79873	74583	34170
hsa-miR-27b-5p	148	173	102	148	102	251	142	255	379	87
hsa-miR-28-3p	141	97	152	195	161	492	127	210	406	64
hsa-miR-28-5p	45	35	95	118	86	215	31	68	212	46
hsa-miR-296-3p	283	381	245	360	292	710	275	375	559	141
hsa-miR-296-5p	283	255	149	270	172	318	226	336	235	63
hsa-miR-29a-3p	33971	25294	23080	46419	15859	38205	39030	69307	41018	38933
hsa-miR-29a-5p	98	100	62	75	58	165	124	218	147	99
hsa-miR-29b-1-5p	188	269	125	210	122	228	200	340	179	114
hsa-miR-29b-2-5p	56	69	63	102	51	91	156	251	86	113
hsa-miR-29b-3p	11176	9598	4613	7731	6368	14548	14366	28529	17894	16662
hsa-miR-29c-3p	1617	1989	1199	3020	1285	2708	4602	7507	2739	5113
hsa-miR-29c-5p	731	1098	924	520	879	1266	1721	2558	1060	1299
hsa-miR-301a-3p	762	435	238	415	556	1150	325	505	601	200
hsa-miR-301a-5p	37	21	15	32	24	62	23	29	30	9
hsa-miR-301b-3p	677	401	302	306	493	1091	252	324	362	120
hsa-miR-30a-3p	85	56	31	144	49	70	101	564	89	38
hsa-miR-30a-5p	1432	276	92	4902	186	172	1742	17199	270	112
hsa-miR-30b-3p	109	74	64	110	106	108	79	148	111	50

hsa-miR-30b-5p	16937	8537	10289	22682	15621	18755	12854	26772	19405	13788
hsa-miR-30c-1-3p	291	352	262	234	225	470	218	255	272	84
hsa-miR-30c-2-3p	2	1	1	24	0	0	6	53	1	0
hsa-miR-30c-5p	39727	29087	33830	42556	27509	60048	41965	45638	30792	17768
hsa-miR-30d-3p	654	385	304	597	662	743	384	834	876	374
hsa-miR-30d-5p	51088	32824	31361	70946	51736	61577	44363	93406	69192	42356
hsa-miR-30e-3p	1874	1776	1383	1389	1640	2788	2215	2766	2164	1230
hsa-miR-30e-5p	122804	93695	35788	108115	76528	182131	116192	159989	159260	95167
hsa-miR-3130-3p	11	24	2	19	14	42	20	21	26	22
hsa-miR-3130-5p	43	35	18	47	21	53	28	52	42	22
hsa-miR-3140-5p	46	38	35	24	30	51	36	61	28	21
hsa-miR-3143	77	21	31	53	31	71	24	36	23	11
hsa-miR-3150b-3p	66	33	46	69	56	71	13	3	67	10
hsa-miR-3158-3p	35	38	22	47	42	99	38	47	64	31
hsa-miR-3168	5	10	100	30	54	15	8	9	3	7
hsa-miR-3176	233	117	123	249	103	294	96	160	204	91
hsa-miR-3181	24	13	33	33	12	43	15	24	37	21
hsa-miR-3187-3p	68	45	36	67	26	69	32	33	39	24
hsa-miR-3194-5p	97	50	44	63	33	85	39	75	78	16
hsa-miR-3195	54	51	26	5	30	47	104	141	84	86
hsa-miR-32-3p	87	65	33	62	55	129	44	76	56	18
hsa-miR-32-5p	2182	1343	822	3103	1360	2315	2238	3257	1901	1058
hsa-miR-320a	6586	9148	6700	12116	5540	13249	11218	13712	7301	3989
hsa-miR-320b	370	376	217	620	163	462	538	750	190	133
hsa-miR-320c	143	138	76	292	33	137	275	401	49	54
hsa-miR-320d	120	118	59	226	23	107	214	330	36	42
hsa-miR-324-3p	964	641	695	550	543	1021	558	859	800	433
hsa-miR-324-5p	2437	1021	1660	2383	1080	2429	1306	2228	1681	1252
hsa-miR-326	229	81	180	151	104	181	141	324	290	81
hsa-miR-328-3p	193	175	203	253	151	323	405	335	160	190
hsa-miR-330-3p	500	335	527	537	342	766	475	570	367	234
hsa-miR-330-5p	1209	564	774	1013	602	1463	714	1026	682	366
hsa-miR-331-3p	1270	1132	780	398	998	1335	1033	2375	1737	1127
hsa-miR-331-5p	177	118	79	117	127	197	133	189	235	76
hsa-miR-335-3p	235	55	48	56	34	55	53	41	29	38
hsa-miR-335-5p	187	64	48	29	54	44	59	72	50	59
hsa-miR-339-3p	3332	3816	2559	4432	2567	5526	3173	3568	4247	1402
hsa-miR-339-5p	3661	2684	1435	2614	1854	3804	2258	3779	3382	1198
hsa-miR-33a-3p	294	118	107	120	141	237	105	186	168	116
hsa-miR-33a-5p	5585	3207	706	733	3097	6172	2590	5165	5970	2981
hsa-miR-33b-3p	378	235	255	256	253	531	122	176	394	137
hsa-miR-33b-5p	1980	787	233	205	696	1746	478	819	1638	650
hsa-miR-340-3p	2	7	117	70	61	128	4	2	74	132
hsa-miR-340-5p	13	3	98	141	98	196	2	7	146	343
hsa-miR-342-3p	79599	54387	108260	39388	90202	111968	47060	62819	61615	19467
hsa-miR-342-5p	198	145	224	286	245	428	198	168	112	36
hsa-miR-345-5p	3621	2266	5452	4593	2985	4754	2588	3212	4018	2119
hsa-miR-34a-3p	645	644	676	687	360	1269	972	1512	715	798
hsa-miR-34a-5p	4078	5162	2574	8860	2710	7098	9550	17416	4118	6336
hsa-miR-34c-3p	2	4	23	8	10	5	11	14	8	76
hsa-miR-34c-5p	9	11	34	27	34	30	10	13	33	195
hsa-miR-3609	27	38	10	41	6	23	65	62	6	14
hsa-miR-361-3p	1410	1166	754	2303	696	1609	2071	3628	1321	1532
hsa-miR-361-5p	6267	4697	7718	5152	6509	11629	5809	6656	5052	2703
hsa-miR-3613-3p	472	367	232	152	242	493	242	452	393	218
hsa-miR-3613-5p	848	556	63	642	387	959	399	1048	587	214

hsa-miR-3614-5p	25	31	32	72	16	38	39	70	35	32
hsa-miR-3615	1044	877	743	1680	558	1106	1340	2013	866	572
hsa-miR-362-3p	81	74	36	138	45	58	51	179	48	48
hsa-miR-362-5p	214	181	138	181	134	263	137	229	183	42
hsa-miR-363-3p	8653	7218	683	8141	2328	3502	7399	8255	1839	1391
hsa-miR-3651	50	61	27	19	39	64	54	80	54	49
hsa-miR-3653-3p	26	24	8	2	12	22	26	58	19	17
hsa-miR-365a-3p	4863	3954	8175	7123	4799	10765	4227	7302	5242	2805
hsa-miR-365a-5p	19	52	18	65	44	58	46	52	13	9
hsa-miR-365b-3p	4863	3954	8175	7123	4799	10765	4227	7302	5242	2805
hsa-miR-3667-3p	46	38	27	25	25	27	19	43	28	23
hsa-miR-3677-3p	56	35	10	69	38	78	19	61	52	14
hsa-miR-3681-3p	11	1	33	15	14	91	11	5	35	19
hsa-miR-3681-5p	166	101	587	234	467	1614	248	92	447	215
hsa-miR-3687	78	66	78	59	63	135	185	245	118	242
hsa-miR-3688-3p	13	14	5	22	15	29	16	43	29	27
hsa-miR-374a-3p	164	130	40	129	138	327	119	205	189	76
hsa-miR-374a-5p	956	744	585	1028	951	1704	1075	1590	862	440
hsa-miR-374b-3p	50	30	22	44	42	83	34	62	47	15
hsa-miR-374b-5p	1885	1456	1560	1554	1345	2678	2218	2864	1701	1113
hsa-miR-374c-5p	77	77	66	12	55	93	90	139	67	66
hsa-miR-378a-3p	28033	27466	26509	35263	26648	56101	31362	51915	40383	19595
hsa-miR-378a-5p	364	602	373	476	415	709	403	964	509	249
hsa-miR-378c	906	619	423	1338	458	1171	879	2017	976	827
hsa-miR-378d	123	99	81	147	93	189	180	330	188	173
hsa-miR-378f	41	37	29	66	37	75	48	85	78	33
hsa-miR-378g	27	24	36	38	33	79	37	58	48	20
hsa-miR-378i	269	274	176	430	162	454	349	738	419	262
hsa-miR-381-3p	1	28	0	56	0	1	15	19	0	0
hsa-miR-383-5p	4	3	141	18	23	5	52	191	4	3
hsa-miR-3909	33	30	53	28	52	124	25	30	40	11
hsa-miR-3912-3p	25	23	21	36	13	33	23	46	27	20
hsa-miR-3916	17	16	19	30	16	27	28	40	15	19
hsa-miR-3928-3p	22	28	23	30	15	52	26	53	32	21
hsa-miR-3940-3p	153	189	73	42	115	118	127	141	108	61
hsa-miR-3960	53	96	15	28	51	55	198	174	61	94
hsa-miR-409-3p	0	16	0	41	0	0	9	4	2	0
hsa-miR-411-5p	0	21	1	49	0	0	11	7	1	0
hsa-miR-421	1256	760	972	1044	999	1961	728	1247	838	413
hsa-miR-423-3p	16201	15362	13995	17149	13094	25399	14129	16118	19973	9522
hsa-miR-423-5p	4721	6786	6521	7618	6908	10579	5592	4717	3532	1859
hsa-miR-424-3p	365	200	82	177	124	108	316	259	122	74
hsa-miR-424-5p	1187	481	226	213	330	432	566	697	362	171
hsa-miR-425-3p	4550	3961	5404	4341	4572	7719	3468	4900	4070	2454
hsa-miR-425-5p	28814	18484	30725	34040	24428	38083	20242	32592	21420	11192
hsa-miR-4284	9	8	7	10	4	5	18	53	4	19
hsa-miR-4286	36700	23034	25200	13344	24421	43353	21033	29059	40945	24157
hsa-miR-4301	37	53	27	11	12	37	65	106	43	64
hsa-miR-4326	357	167	223	328	175	359	152	289	220	118
hsa-miR-4443	59	49	29	68	42	103	81	71	23	21
hsa-miR-4446-3p	42	30	37	36	24	45	22	41	18	12
hsa-miR-4448	5613	4956	4142	6816	4046	8364	6631	6846	5653	4198
hsa-miR-4449	104	99	41	35	51	79	134	203	91	82
hsa-miR-4454	9377	5889	10412	4006	9955	11905	5844	7752	8939	6351
hsa-miR-4455	207	189	291	463	298	530	200	196	249	111
hsa-miR-4461	44	33	28	102	12	37	57	99	65	46

hsa-miR-4473	52	33	30	46	30	52	26	80	39	29
hsa-miR-4485-3p	796	2589	410	560	198	475	3262	6139	307	892
hsa-miR-4488	156	162	67	66	170	248	497	384	241	308
hsa-miR-4491	19	17	12	30	37	42	14	32	33	14
hsa-miR-4497	4	15	10	14	7	10	30	55	8	31
hsa-miR-4508	13	31	18	32	18	36	70	56	35	38
hsa-miR-450a-5p	360	93	54	97	63	100	125	166	78	31
hsa-miR-450b-5p	147	39	29	31	44	51	32	41	42	11
hsa-miR-4517	35	48	41	64	30	52	49	61	52	33
hsa-miR-4518	16	21	15	15	7	68	4	20	3	22
hsa-miR-4521	151	127	136	308	108	267	85	178	193	149
hsa-miR-4524a-3p	21	44	13	24	7	21	30	30	23	20
hsa-miR-4524a-5p	66	46	40	56	20	75	29	36	55	34
hsa-miR-4532	2110	1896	1167	274	1924	2248	6691	7367	3782	4502
hsa-miR-454-3p	831	587	465	1012	529	1081	618	1102	645	319
hsa-miR-454-5p	291	181	172	160	162	369	113	168	199	64
hsa-miR-455-3p	9	25	2	2	2	0	64	17	2	1
hsa-miR-4659a-3p	94	79	146	115	81	166	74	72	127	37
hsa-miR-4659b-3p	28	10	39	28	29	33	22	22	51	18
hsa-miR-4677-3p	142	117	126	159	134	201	111	205	145	87
hsa-miR-4746-5p	45	64	53	42	49	90	19	38	53	14
hsa-miR-4767	221	216	108	490	136	300	305	510	300	263
hsa-miR-4772-5p	29	4	20	7	6	60	20	13	32	4
hsa-miR-4791	12	6	6	18	9	20	28	46	13	14
hsa-miR-4792	100734	75561	50084	34210	69955	94373	236635	171618	52886	59561
hsa-miR-484	6101	4494	3868	6614	3334	7138	3012	5521	5253	2418
hsa-miR-486-3p	180	403	7	373	147	308	283	316	160	167
hsa-miR-486-5p	7363	9767	1407	10373	3734	7204	5346	6976	3082	1738
hsa-miR-491-5p	69	32	42	41	51	89	34	93	57	24
hsa-miR-497-5p	29	27	39	19	34	69	21	24	48	19
hsa-miR-5001-3p	82	35	64	74	27	72	55	73	79	34
hsa-miR-500a-3p	926	907	1093	1035	805	1136	788	1264	844	420
hsa-miR-500a-5p	62	39	26	53	24	62	28	61	41	17
hsa-miR-501-3p	497	543	617	588	506	664	489	759	489	238
hsa-miR-501-5p	50	47	24	64	26	50	31	58	36	10
hsa-miR-5010-3p	56	48	41	66	45	74	55	72	53	42
hsa-miR-502-3p	308	240	193	270	122	285	201	422	268	139
hsa-miR-503-5p	204	84	45	110	48	74	66	90	48	35
hsa-miR-505-3p	1398	593	761	688	703	1467	438	886	943	312
hsa-miR-505-5p	160	79	83	81	95	138	61	95	72	17
hsa-miR-5094	43	24	51	56	33	53	48	53	29	23
hsa-miR-5096	61	53	54	67	45	64	49	82	65	38
hsa-miR-5100	1224	967	461	687	983	1232	670	1007	1362	667
hsa-miR-513c-5p	4	3	3	10	1	5	52	53	0	9
hsa-miR-532-3p	168	234	158	171	134	191	182	342	182	88
hsa-miR-532-5p	929	614	438	960	437	968	622	1080	863	274
hsa-miR-542-5p	44	12	7	9	11	24	22	24	9	2
hsa-miR-545-3p	441	295	111	167	444	685	369	574	407	172
hsa-miR-548aa	192	140	150	104	99	231	115	161	117	79
hsa-miR-548ad-5p	115	76	56	81	60	121	49	92	87	28
hsa-miR-548ae-5p	115	76	56	81	60	121	49	92	87	28
hsa-miR-548ah-3p	158	19	24	12	13	60	12	26	79	7
hsa-miR-548ah-5p	101	3	3	1	4	17	3	11	23	2
hsa-miR-548aj-5p	401	182	150	302	144	368	148	220	257	226
hsa-miR-548am-5p	124	59	55	69	52	121	67	104	106	50
hsa-miR-548ap-3p	83	57	63	42	49	84	54	67	39	29

hsa-miR-548aq-3p	52	46	33	24	30	42	34	34	39	15
hsa-miR-548ar-5p	401	181	150	302	144	368	148	219	257	226
hsa-miR-548aT-5p	124	59	55	69	52	121	67	104	106	50
hsa-miR-548av-3p	71	67	51	67	71	99	47	63	80	19
hsa-miR-548av-5p	341	234	225	248	227	470	146	264	311	100
hsa-miR-548ay-5p	115	76	56	81	60	121	49	92	87	28
hsa-miR-548c-5p	124	59	55	69	52	121	67	104	106	50
hsa-miR-548d-3p	123	63	48	45	49	97	33	72	72	27
hsa-miR-548d-5p	115	76	56	81	60	121	49	92	87	28
hsa-miR-548e-3p	309	142	146	263	154	420	141	216	284	162
hsa-miR-548e-5p	152	71	70	83	73	186	48	86	110	40
hsa-miR-548f-3p	96	47	37	64	52	165	19	57	72	41
hsa-miR-548f-5p	382	165	142	275	138	346	132	200	246	219
hsa-miR-548g-5p	401	182	150	302	144	368	148	220	257	226
hsa-miR-548h-3p	268	190	158	251	163	331	176	308	219	112
hsa-miR-548h-5p	384	168	142	273	140	343	132	204	248	219
hsa-miR-548k	341	234	225	248	227	470	146	264	311	100
hsa-miR-548l	41	39	19	36	26	42	22	33	27	11
hsa-miR-548o-3p	71	67	51	67	71	99	47	64	80	19
hsa-miR-548o-5p	124	59	55	69	52	121	67	104	106	50
hsa-miR-548p	157	21	28	17	15	67	13	29	78	7
hsa-miR-548s	46	19	24	29	22	45	13	20	8	3
hsa-miR-548t-3p	192	140	150	104	99	231	115	161	117	79
hsa-miR-548w	106	46	69	90	45	148	59	102	80	41
hsa-miR-548x-5p	401	182	150	302	144	368	148	220	257	226
hsa-miR-548z	268	190	158	251	163	331	176	308	219	112
hsa-miR-550a-3-5p	41	105	50	40	35	94	41	26	40	29
hsa-miR-550a-3p	156	236	121	173	75	182	100	100	139	112
hsa-miR-550a-5p	41	105	50	40	35	94	41	26	40	29
hsa-miR-551b-3p	341	413	124	353	58	51	420	1102	126	531
hsa-miR-551b-5p	452	1096	422	950	156	128	785	1472	222	477
hsa-miR-5680	17	57	14	55	8	18	87	95	11	1
hsa-miR-570-3p	66	40	36	14	53	73	36	49	40	14
hsa-miR-5701	10	20	8	4	9	25	17	44	18	24
hsa-miR-574-3p	110	127	173	122	103	349	134	158	182	90
hsa-miR-574-5p	74	70	51	57	67	100	140	111	33	19
hsa-miR-576-3p	101	65	56	54	70	148	43	74	123	31
hsa-miR-576-5p	888	652	623	784	524	903	525	909	843	477
hsa-miR-577	156	194	161	325	153	64	61	89	38	3
hsa-miR-582-3p	31	31	21	18	24	45	33	38	39	15
hsa-miR-582-5p	97	68	81	64	62	133	99	146	124	48
hsa-miR-589-3p	63	26	34	58	53	100	30	43	69	25
hsa-miR-589-5p	902	816	893	1146	1005	1783	493	851	1079	614
hsa-miR-590-3p	755	379	214	540	424	1104	343	671	587	322
hsa-miR-590-5p	72	70	31	24	58	119	51	117	96	52
hsa-miR-598-3p	134	102	69	193	57	180	145	252	112	72
hsa-miR-6087	530	652	215	152	432	615	1446	2281	490	1129
hsa-miR-615-3p	86	700	48	259	133	17	451	824	293	31
hsa-miR-616-5p	152	114	112	166	78	231	157	210	139	83
hsa-miR-618	206	75	85	216	8	47	200	513	35	3
hsa-miR-619-5p	136	154	132	151	124	222	196	238	179	169
hsa-miR-624-5p	72	48	62	70	76	107	49	92	76	35
hsa-miR-625-3p	2068	1700	1052	1413	940	2345	1194	1617	1928	1223
hsa-miR-625-5p	10026	7397	7002	5528	4685	12827	5911	6079	7692	4640
hsa-miR-627-3p	36	25	16	31	21	44	24	27	34	14
hsa-miR-627-5p	33	25	19	36	20	51	24	34	30	16

hsa-miR-628-3p	179	189	146	128	137	261	250	370	156	124
hsa-miR-628-5p	26	17	24	29	21	45	48	40	28	10
hsa-miR-629-3p	60	88	39	75	53	44	60	72	68	37
hsa-miR-629-5p	615	604	173	688	274	496	443	563	608	213
hsa-miR-641	403	347	311	272	311	586	345	366	403	150
hsa-miR-642a-3p	168	228	253	220	205	228	219	163	245	68
hsa-miR-642a-5p	217	287	164	208	154	196	248	329	265	86
hsa-miR-651-5p	22	21	15	42	28	43	23	43	31	13
hsa-miR-652-3p	2955	1810	4255	3577	2307	3122	2182	2778	4102	2250
hsa-miR-652-5p	89	47	51	83	61	101	58	86	151	70
hsa-miR-659-5p	28	11	28	28	15	41	28	42	43	23
hsa-miR-660-5p	491	353	264	565	257	574	490	924	559	222
hsa-miR-663a	5	8	10	2	10	13	38	37	24	41
hsa-miR-664a-3p	231	237	307	350	190	304	439	691	246	374
hsa-miR-664a-5p	247	178	402	387	200	261	548	594	288	382
hsa-miR-664b-3p	13	12	12	23	13	25	28	45	20	17
hsa-miR-671-3p	718	852	766	932	732	1563	815	928	1182	486
hsa-miR-671-5p	435	285	202	399	265	738	268	380	409	234
hsa-miR-6724-5p	82	92	59	137	39	72	93	148	109	76
hsa-miR-6842-3p	49	20	61	57	33	63	50	43	68	32
hsa-miR-6881-3p	34	20	29	53	16	44	45	52	17	19
hsa-miR-7-1-3p	840	825	722	957	540	1122	896	1512	1116	769
hsa-miR-7-5p	7060	4939	1939	7360	2756	8957	3868	8152	5880	4011
hsa-miR-708-5p	9	59	1	2	2	0	4	11	3	0
hsa-miR-744-3p	57	21	47	31	31	92	29	36	49	11
hsa-miR-744-5p	1105	793	1181	1141	796	1853	767	994	957	415
hsa-miR-7641	522	662	320	211	279	565	2847	2350	454	1333
hsa-miR-766-3p	933	751	669	301	695	576	256	599	615	251
hsa-miR-766-5p	184	92	93	141	75	111	75	119	65	29
hsa-miR-769-3p	76	64	75	85	61	141	80	156	102	51
hsa-miR-769-5p	3117	1898	2216	2416	1994	4468	1976	3373	3228	1960
hsa-miR-7704	74	92	64	67	68	122	207	212	110	132
hsa-miR-7706	176	184	274	301	179	251	168	274	217	103
hsa-miR-7974	1599	1241	1260	1248	873	2319	537	850	1612	657
hsa-miR-7976	80	74	53	37	46	80	31	55	65	40
hsa-miR-7977	10841	11580	8327	6955	11494	14521	7167	9413	14477	7561
hsa-miR-874-3p	5484	3946	4963	2715	4889	6507	2338	3174	7034	2191
hsa-miR-874-5p	258	171	166	166	192	358	102	168	389	127
hsa-miR-877-5p	35	31	32	54	49	72	62	21	11	2
hsa-miR-9-3p	93	74	110	153	155	143	116	191	97	53
hsa-miR-9-5p	778	1049	709	1683	1340	830	2161	3414	535	337
hsa-miR-92a-1-5p	1822	2728	1324	2112	1163	2667	1178	1606	2365	982
hsa-miR-92a-3p	126047	153805	101536	177122	89715	173764	99810	133898	155463	77795
hsa-miR-92b-3p	2193	2619	968	1350	665	1273	1286	1195	1084	1034
hsa-miR-93-3p	570	399	505	315	369	804	207	285	527	133
hsa-miR-93-5p	14202	11662	8691	16282	10154	17933	9946	14949	11430	3962
hsa-miR-940	63	80	93	103	103	182	54	76	97	35
hsa-miR-941	1186	1126	1291	1438	1590	2571	777	1051	1701	436
hsa-miR-942-3p	70	58	48	32	35	91	19	43	74	17
hsa-miR-942-5p	787	821	757	864	532	1175	557	758	682	344
hsa-miR-944	30	28	19	24	72	44	59	192	37	78
hsa-miR-96-5p	73	72	28	42	74	18	66	109	83	52
hsa-miR-98-3p	456	303	550	222	399	1044	378	422	326	191
hsa-miR-98-5p	6736	6462	5997	7408	5578	9754	5730	10977	4898	2606
hsa-miR-99a-5p	48	76	213	467	190	993	469	570	379	42
hsa-miR-99b-5p	591	1645	1831	1713	561	139	1837	709	337	111

miRNA	logFC	logCPM	PValue
hsa-miR-340-5p	4.438	2.939	1.583E-12
hsa-miR-340-3p	4.818	2.675	5.072E-10
hsa-miR-190a-3p	-9.098	2.902	6.203E-10
hsa-miR-3168	3.338	2.389	9.091E-06
hsa-miR-33a-5p	-2.276	8.820	3.207E-05
hsa-miR-190a-5p	-3.825	2.183	1.428E-04
hsa-miR-4485-3p	-2.477	8.397	3.676E-04
hsa-miR-6087	-2.400	7.015	4.413E-04
hsa-miR-3960	-2.446	3.875	6.382E-04
hsa-miR-151b	1.609	7.049	1.263E-03
hsa-miR-7641	-2.284	7.450	2.486E-03
hsa-miR-28-5p	1.484	3.434	2.935E-03
hsa-miR-455-3p	-3.663	1.813	3.036E-03
hsa-miR-33b-5p	-1.973	6.857	3.175E-03
hsa-miR-151a-5p	1.676	11.169	3.188E-03
hsa-miR-205-5p	-4.381	11.433	3.596E-03
hsa-miR-4488	-1.942	5.104	4.121E-03
hsa-miR-4532	-2.215	8.931	5.110E-03
hsa-miR-3681-5p	1.717	5.402	5.617E-03
hsa-miR-10b-5p	-2.404	5.096	6.273E-03
hsa-miR-424-5p	-1.500	6.441	6.433E-03
hsa-miR-545-3p	-1.393	5.634	7.056E-03
hsa-miR-4792	-1.519	14.080	7.444E-03
hsa-miR-4449	-1.555	3.991	8.750E-03
hsa-miR-708-5p	-3.687	1.432	8.904E-03
hsa-miR-3195	-2.082	3.308	9.368E-03
hsa-miR-34c-5p	1.738	1.675	1.169E-02
hsa-miR-3653-3p	-2.356	1.963	1.285E-02
hsa-let-7b-3p	1.535	3.580	1.480E-02
hsa-miR-3681-3p	2.066	1.306	1.695E-02
hsa-miR-345-5p	1.034	9.217	2.068E-02
hsa-miR-29b-3p	-1.139	10.872	2.442E-02
hsa-miR-135b-5p	-2.436	2.768	2.495E-02
hsa-miR-4455	1.069	5.387	2.510E-02
hsa-miR-548ah-5p	-3.491	1.759	3.258E-02
hsa-miR-652-3p	0.946	8.902	3.664E-02
hsa-miR-615-3p	-1.719	5.912	3.796E-02
hsa-miR-138-1-3p	1.139	6.996	3.820E-02
hsa-miR-204-5p	-1.975	2.854	3.952E-02
hsa-miR-212-5p	1.626	4.001	4.142E-02
hsa-miR-4301	-1.431	2.989	4.256E-02
hsa-miR-365a-3p	0.865	9.905	4.492E-02
hsa-miR-365b-3p	0.865	9.905	4.494E-02
hsa-miR-590-5p	-1.212	3.264	4.578E-02
hsa-miR-151a-3p	1.147	7.323	4.715E-02

miRNA	logFC	logCPM	PValue
hsa-miR-196b-5p	4.173	5.287	4.090E-04
hsa-miR-551b-3p	-3.022	5.845	4.264E-04
hsa-miR-10b-5p	-4.443	4.230	2.157E-03
hsa-miR-3681-5p	1.707	6.383	4.453E-03
hsa-miR-196a-5p	-4.245	3.640	4.745E-03
hsa-miR-205-5p	-4.097	6.872	5.099E-03
hsa-miR-551b-5p	-2.176	6.462	5.862E-03
hsa-miR-4485-3p	-2.201	7.486	6.045E-03
hsa-miR-199b-3p	-2.324	2.802	6.278E-03
hsa-miR-199a-3p	-2.324	2.802	6.532E-03
hsa-let-7b-5p	2.090	6.998	6.732E-03
hsa-miR-3168	2.427	1.857	6.903E-03
hsa-miR-143-3p	-2.745	8.193	1.036E-02
hsa-miR-190a-5p	-3.138	0.979	1.636E-02
hsa-miR-3909	1.361	3.097	1.669E-02
hsa-miR-342-5p	1.299	5.077	1.832E-02
hsa-miR-146b-3p	-1.392	6.170	1.844E-02
hsa-miR-192-5p	-2.204	10.177	1.959E-02
hsa-miR-99a-5p	1.739	5.491	2.001E-02
hsa-miR-145-5p	-2.744	3.608	2.075E-02
hsa-miR-127-3p	-4.183	3.102	2.630E-02
hsa-miR-10a-5p	-1.921	12.453	3.040E-02
hsa-miR-383-5p	2.045	0.834	3.190E-02
hsa-miR-204-5p	-3.308	1.650	3.199E-02
hsa-miR-708-5p	-3.924	1.435	3.508E-02
hsa-miR-92b-3p	-1.122	8.131	3.758E-02
hsa-miR-342-3p	0.827	13.604	3.840E-02
hsa-miR-221-5p	-2.035	7.619	3.958E-02
hsa-miR-138-1-3p	1.063	6.887	4.186E-02
hsa-miR-10a-3p	-2.087	4.104	4.220E-02
hsa-miR-1275	1.228	5.315	4.277E-02
hsa-miR-4301	-1.529	3.132	4.292E-02
hsa-miR-181a-3p	-1.410	7.217	4.432E-02
hsa-miR-877-5p	1.514	2.621	4.657E-02
hsa-miR-191-5p	0.775	15.684	4.826E-02
hsa-miR-192-3p	-2.398	2.710	4.876E-02